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DR. THEODORE G. KLUMPP, President,
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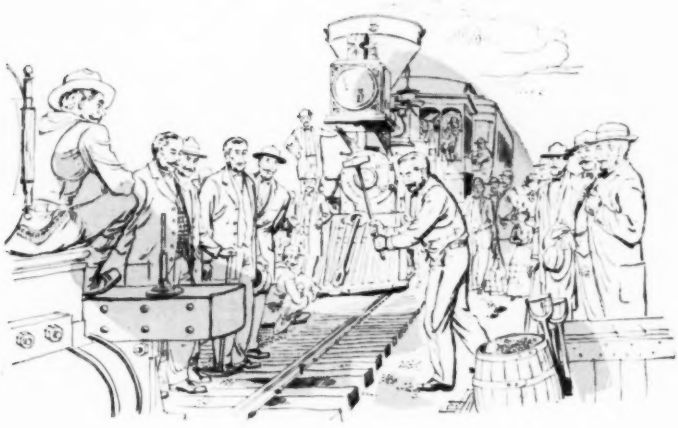

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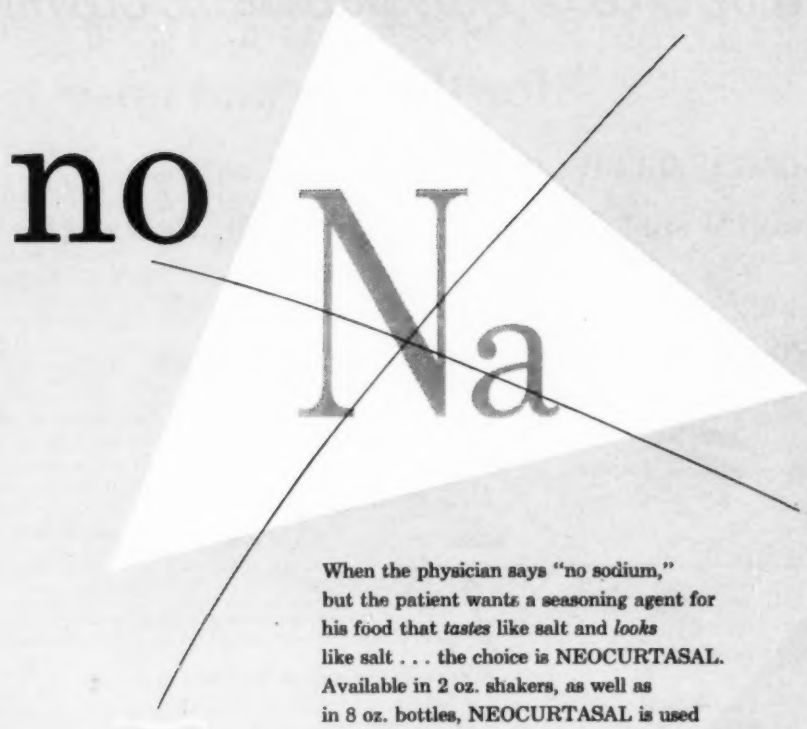

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E D I T O R I A L

THIS issue of the *Journal* is devoted largely to some of the many excellent papers presented at the mid-year convention of the American Pharmaceutical Manufacturers' Association, held in New York, December 6-8, 1948.

In place of our customary editorial we are preceding these papers with the address of the Association president, Dr. Theodore G. Klumpp. This address without doubt is far better in its thought provoking qualities than any editorial we might present. Dr. Klumpp's concern over certain current trends affecting pharmacy is well-founded. It is unfortunate that more leaders in our field do not sense the same imperative need for action while there is still time. When one appreciates the long struggle which man made for personal liberty and freedom it is tragic indeed to see civilization frittering away these hard won gains. Slowly but surely, however, we are becoming a regimented society with regulations and restrictions burdening and limiting our actions, every day a little more. So insidious are these changes that they are given but scant consideration by most people and only too late will their full significance be recognized; thus has freedom been lost before. We can but add our small voice to the warnings issued by Dr. Klumpp. We do not know whether he shares our pessimism concerning the future but we, at least, support his views on the seriousness of the current situation as well as the general apathy concerning it.

L. F. TICE

PRESIDENTIAL ADDRESS

American Drug Manufacturers' Association

By Theodore G. Klumpp, M. D.

WE have made great progress in the last two decades in advancing pharmaceutical research and providing the medical profession with new medicaments to conquer disease. I am happy to note that we have become research conscious and have seen the wisdom of spending a substantial proportion of our income for the development of new drugs.

For generations Europeans and particularly the Germans were the leaders in pharmaceutical research. We have taken the lead from the Germans and I don't think they will ever get it back. This is not because we won the war and the Germans lost it. We were ahead of the Germans in pharmaceutical research when the Germans were winning the war and the Allies were losing it. The commercial production of penicillin was perfected by us while the Germans were at the mightiest peak of their power. We developed a dozen sulfa drugs while the Germans produced only two or three. But more important than all of this, we show signs of having caught on to the knack of research. We now have more antibiotics than we know what to do with and as far as large scale production of drugs is concerned we now occupy the place in the world that our former enemies held almost without challenge. We have learned to produce drugs cheaply too. Who in 1942 would have dreamed of life-saving penicillin at less than twenty cents per 100,000 units? You will recall that this same drug sold at eighteen dollars per 100,000 units only 5 years ago.

One of the best indications of the healthy state of our industry, as far as research is concerned, is our recent experience with the antihistaminic drugs. Two years ago there were two such drugs on the market; today there are so many that doctors and pharmacists are complaining that they cannot keep up with them. The production of streptomycin is another example of the virility of our industry. There were those who attributed our remarkable record with penicillin to the stimulus of war and the support of the government. If you will compare the production records of penicillin and streptomycin you will find that under a system of completely free enter-

prise streptomycin is ahead of penicillin's record in meeting the respective requirements for these drugs. It is true that we learned something from our penicillin experience, but since then we have demonstrated that this industry can stand on its own feet and produce not only our nation's requirements but the world's requirements of important drugs without governmental help or subsidy.

Our industry also has reason to be proud of its record during this period of inflation. Prices of drugs have risen very little and a statistical study of this will, I am sure, show that no industry has done a better job in this respect than we.

But I am convinced that we and the medical profession have failed to show the public why they cannot expect a surgical operation for the price of a hair cut. We have not succeeded in demonstrating that if a pound of candy at a dollar and a half is reasonable then a simple prescription at the same price or twice that amount is not highway robbery. If a dinner and an evening's entertainment for ten dollars or fifteen is not unreasonable then there should be no real resentment when a physician charges the same amount for a service that may save the individual's life.

While this applies to many Americans today it is of course recognized that there are some who cannot afford the price of any catastrophe whether it be a broken arm or a wrecked automobile. Nevertheless, the fact remains that the public and the medical profession regard the cost of drugs as high. With this in mind I have wondered whether or not it is good public policy for pharmaceutical houses to vie with one another in displays of affluence. What I refer to are the expensive parties, extravagant entertaining of doctors, the excessively costly house organs, luxury advertising, expensive souvenirs, and torrents of samples that inevitably lead to the question, "If these houses can afford to splurge this way, why don't they cut the price of their drugs a little instead?" I believe in the economic justification of house organs, samples and first class advertising but there is a real danger, if the present trend continues, that competition in these matters will be pitched at a level of cost that will be regarded as wasteful by the medical profession. We are, after all, not venders of luxuries, and our store-windows should not look like Fifth Avenue before Christmas.

For almost eight years the industry has had an exceedingly difficult time with solutions for injection. During this time splendid

progress has been made in manufacturing solutions ever better in quality. To this extent the efforts of the Food and Drug Administration have had a commendable effect. However it is clear to me, as it is to everyone else in the industry who has been intimately concerned with the problem, that the government has set a standard that cannot be attained by the industry generally under conditions of good pharmaceutical practice, nor consistently by individual manufacturers, even those who have exhausted every resource that money and technical skill can provide. The issue is not the public safety and welfare. There can be no compromise on that and this industry is proud of its record in this respect. We are concerned here with an academic utopia which good manufacturing practice has not yet attained. Furthermore I don't think our industry can or ever will be consistently able to produce "optically empty" injections.

The last Revision Committee of the United States Pharmacopoeia tried to ameliorate this situation by setting a standard for injections so that they would be "substantially free" of undissolved material. It was hoped that this would serve as a reasonable basis for judging whether or not such solutions are in violation of the law. This hope has not been realized. I have taken the trouble to examine many solutions on the market. I am convinced that at the present time the Food and Drug Administration is in effect objecting to many solutions that are the products of "good pharmaceutical practice" and entirely safe and suitable for the purpose for which they are distributed.

The Committee on Revision of the U. S. P. and the National Formulary have it within their power to ameloriate the present unsatisfactory state of affairs. At the time this problem was considered some six years ago, I proposed that the official compendia introduce the concept of "good pharmaceutical practice" into their standards. I am still convinced that the idea is a good one and I urge them to again consider it. Some such expression as "solutions shall be substantially free of undissolved material when judged in the light of good pharmaceutical practice as a criterion" would help. Previously there were objections to this statement as being too indefinite. To this I can only reply that I know of no more precise standard that will serve for the entire gamut of injections. If anyone has something more definite I am sure that all concerned would be glad to hear about it. Such a statement has at least this virtue that the manufacturer has

an equal opportunity with the government to make a showing in court or any other place as to what constitutes "good pharmaceutical practice." That is at least something more definite than we now have.

Some have said that there is no solution to the problem until we have an electronic machine to set our standard for us. This is, I am convinced, an utterly unrealistic approach to the problem. In the first place, the machine is not now available and will probably not be for another five or six years, secondly, there is nothing magic about such a machine. It must also be set on the basis of standards that we can agree on and meet. It must also in the last analysis set a standard based on what the industry can do under conditions of "good pharmaceutical practice." There is no escaping this whether we use the human eye, an electronic machine or even an atomic pile to test our solutions.

The pharmaceutical industry has a grave responsibility to the public and the medical profession. Upon its care, skill and accuracy rests the safety and welfare of those who take drugs and the confidence of those that prescribe them. Unless we do a good job the knowledge and skill of the medical profession is of little avail. Our industry is keenly aware of this and it is proud of its record. On the other hand, those that operate airlines and railroads and those that build bridges, skyscrapers and elevators have a similar responsibility. Mistakes and carelessness in any of these fields may have equally serious consequences. But as far as I know only those functioning within the jurisdiction of the Food, Drug and Cosmetic Act are singled out for extraordinary or unusual penalties under this statute. In all other fields when an accident occurs the individual or the corporation presumably responsible is subject to criminal penalties only when criminal negligence has been shown. In our industry an accident, failure of equipment, a technical and sometimes unimportant variation from a standard that is not infrequently even in itself difficult to determine may lead to criminal penalties. Intent or criminal negligence has nothing to do with crime as far as we are concerned. When viewed from the standard of American jurisprudence the criminal sections of the Food, Drug and Cosmetic Act are extraordinary. For over fifteen years I have been surprised that the food and drug industries have submitted to this legislative discrimination so meekly.

I refer to this merely to record the fact that I consider this aspect of the law basically and constitutionally unfair. I recognize all too well that there are "tides in the affairs of men" and I don't think the tide is right now for our industries to attempt to correct this inequity.

There is, however, a legislative inequity which, in my opinion, warrants prompt and decisive action on the part of all those concerned. I refer to the exceedingly unfair rules under which the Federal Trade Commission operates. It is truly extraordinary to me that a liberty loving people are willing to countenance a procedure in which a governmental agency is judge, jury and prosecutor all in the same role. As un-American as this is it is only surpassed by the legal principle which makes it necessary for the actions of the Federal Trade Commission to be supported only by evidence of record. Mind you, the Commission doesn't have to have a preponderance of evidence nor even a balance of evidence, it just has to have evidence. A correction for this was introduced into the last Congress as the O'Hara Bill. It merits further consideration and I hope our industry will encourage the re-introduction of the O'Hara bill when the Congress reconvenes.

The governmental drive against patents continues. Undoubtedly there were certain abuses of the patent monopoly that required correction, but there are those who want to scuttle the ship because there is a rat aboard. The stimulus to invention of the patent system has recently been again forcefully demonstrated in the drug industry. The invention of a new antihistaminic resulted rather promptly in the invention of almost a score of other drugs of the same class. If the first antihistaminic had been available to the entire drug industry through compulsory licensing, I seriously doubt that the other firms would have spent the same amounts for research in this field. It would have been cheaper for them to take a license and save the research expenditures. But through the operation of our patent system there will emerge better antihistamine drugs than the first ones invented and the public will be the direct benefactor of this stimulus to invention.

One of our largest chemical concerns recently announced that it was offering general licenses to a large number of its process patents. This was presumably done under governmental pressure, if not directly at least indirectly.

What is the effect of this on chemical progress? You don't have to be a patent expert to figure out what will happen. When compulsory licensing of process patents is in vogue there just won't be any patents. The manufacturing chemists will keep their processes secret and the knowledge that should be made generally available and eventually utilizable by everybody will never see the light of day.

I am afraid that if all the reformers working on us have their way we will be an industry in which everybody sells the same thing, at the same price, pays the same wages, gives the same discounts, employs the same labels, and promulgates the same advertising. That will be a jolly state of affairs and competition will be based on who likes whom rather than on research, distinctive products, and service.

There is no doubt about it but living has grown increasingly more complex in these forty-eight United States of ours. This is especially true for the business man and his organization. Federal, state and municipal regulation and taxation has grown increasingly complicated and in some instances these have become conflicting, contradictory, overlapping and in many cases they have had an unnecessarily restrictive effect upon the normal growth and development of business. Sales taxes, use taxes and laws relating to doing business in the various states are such that a corporation can no longer get along without the services of a large staff of legal, tax and accounting experts. In more instances than are wholesome for our economy, business decisions must be based on tax and accounting considerations, rather than on the best interests of the business or the public we serve. In other fields regulations have also grown complicated and contradictory to the point where it is well nigh impossible to reconcile business interests with them. To cite an example; my company markets a disinfectant. One agency of the federal government requires certain directions for use; another tells us they are unnecessary, and a third agency (this time a state) will not permit the product to be sold if we follow the requirements of the first agency.

I have had the privilege of viewing our industry from the standpoint of a governmental official. I have also seen it in operation from the inside. From both points of view it has always seemed to me that the industry lacks unity. I am sorry to have to say it but there is something lacking. I see little evidence of statesmanship in our

family. We don't seem to be able to get together promptly and decisively in representing the industry's point of view. It takes more money and a larger staff than any of our trade associations now possess to fight the industry's battles in Washington, in the forty-eight states, and the many municipalities that are regulating us. The voice of the industry is rarely heard. When state legislatures consider bills, having an effect upon us, writing a letter is not enough. We should have a competent representative present to speak our views. As a result, the web of restrictive legislation and regulations has tightened around us until we feel like Simeon Clay:

The Government gave Simeon Clay
Terrific headaches by the way
It made him fill out numerous blanks
Without a single word of thanks.
It even threatened, stern and grim,
To fine and/or imprison him
If he omitted to compile
The schedules which it loved to file.

Clay looked around, saw it was worse
And even harder on the purse
In England, Finland, Yap, Siam,
The Argentine, and parts of Guam.
So off he went, a week ago,
To turn into an Eskimo,
Far in the North, where cross officials
Will shriek in vain for his initials,
And where he will ignore their wishes
And live on ice and little fishes.

A few years ago it did not matter so much, each one of these things was looked upon more or less as a tax upon doing business but costs have risen and profit margins have declined to the point where a day will come, and it may not be far off, where we will not be able to afford the luxury of always turning the other cheek. I am certain that we cannot raise prices to meet the increased costs of doing business. Rightly or wrongly the public has the impression that drug prices are already too high.

When future historians look back upon this post war period in which we in the United States are now living they will, I venture to say, classify it as a time of great prosperity, an era of well being. And why shouldn't they? We have an all time employment record, over 62 million gainfully employed. The income of farmers and industrial workers is at an all time high. Despite high prices no one is starving and the standard of living of all of our people is at a level never before attained in the history of the world.

And yet many of us living through this era don't feel comfortable about it. We don't enjoy the prosperity we are supposed to be enjoying. And the reason is that we think it is not a sound, healthy and enduring prosperity. We see ourselves an oasis of plenty in a bankrupt world. Our riches have been borrowed from the frightful destruction of the most devastating war the world has ever known, and despite present appearances to the contrary, it is a simple axiom that true and enduring wealth springs from creative effort not from the ashes of death, ruin and destruction. Some of us are uneasy too because it is all too clear now that the last war did not bring the peace and freedom to the world for which we fought. There is still war in China, in Germany, in Greece, in the Balkans, in Asia; and the war clouds are gathering, rather than dispersing. And above it all hovers the atomic bomb with the world fiddling while Russian scientists burn the midnight oil perfecting their own bomb. Can you understand why some of us are not happy about the shape of things to come?

As I view world events during the last three decades I cannot escape the conviction that the world is moving in a long and continuous cycle toward statism, socialism, fascism, or whatever other specific term you want to apply to it. The least common denominator of the movement is that freedom and liberty are progressively disappearing throughout the world and the governors of the world are steadily increasing their power over the governed. In some countries dictators wrest power from their subjects by force; in other countries the people are content to vote more and more power to their governments, a ritual in which they exchange freedom for security. Some of this is inevitable amid the complications of our modern society. But the important point is that I am not sure that we are going to be smart enough to know where to stop any more than the Bolsheviks knew where to stop. I don't think we realize,

as Winston Churchill put it, "that in a democracy there is unequality of wealth and happiness; under communism there is equality of poverty and unhappiness."

A conspicuous part of this world movement is the spread of socialism, paternalism and nationalization in Great Britain. There are strong advocates of the same trend in this country and during the next four years we may expect to see a powerful drive here for essentially the same things that they have in Great Britain.

We are particularly concerned with the effect on the medical profession and the practice of medicine. Socialized medicine in Great Britain is getting off to a booming start. For the first three months of operation under the National Health Service Act and before the scheme had gotten fully underway and was fully exploited the cost was fifty-two million pounds (52,000,000) or just about twice the amount forecast. Already serious abuses have been reported. It has been found, for instance, that patients are cashing in prescriptions for a fraction of their value for cosmetics and other items. An exodus of younger physicians to the English colonies has also been noted and some doctors are reported so overworked that they cannot give proper attention to their practice. At the same time the drug and pharmaceutical business is for the moment experiencing a real boom. I hope that none of our industry in this country will be misled by this which is nothing more than the feverish flush of a sick patient. In order to cut down on costs the Ministry of Health will certainly crack down on the drug and dental industries.

First there will be restrictions on prescriptions, limiting the practitioner to those items appearing on an approved list. This will have the effect of sharply limiting the use of certain specialties and some of the proprietaries. If this doesn't achieve the desired effect we may anticipate nationalization of the drug and pharmaceutical industries about which there is already talk in Great Britain. We have a grave responsibility to our public and to ourselves to do everything we can to resist the grafting of the same socialistic or communistic philosophy, if you will, into the sturdy trunk of our American democracy. It is only by being aware of what is going on in the world that we have any chance at all of stopping it. Paradoxically it was a German, Goethe, who said, "Only the man deserves his life and freedom who daily conquers them anew."

BASIC RESEARCH IN THE FIELD OF BLOOD DISORDERS*

By Roy R. Kracke, M. D.**

BASIC research in this field continues to make satisfactory progress. This is particularly true in the field of anemias, not only because of the advent of folic acid but more recently because of the discovery of Vitamin B_{12}. All anemias can be roughly divided into four large groups, these being the iron deficiency anemias, the macrocytic types, the hemolytic anemias, and the refractory group of marrow aplasia.

With respect to the iron deficiency group, there has not been substantial progress in this field within recent years, although considerable fundamental knowledge continues to accumulate, with particular reference to the metabolism of iron, and further progress is promised by the use of tracer studies with tagged materials. The treatment of iron deficiency anemias remains essentially the same. There seems general agreement that nearly all of these patients should be treated with ferrous sulfate. In some patients who cannot tolerate this preparation it still can be given in very small divided doses, spread over a great many hours each day. There seems little indication for the use of any other preparation and there is certainly no indication for the use of iron by parenteral methods.

The treatment of the macrocytic anemias, or those that are accompanied by a megaloblastic bone marrow, is in a state of rapid change. In order to properly treat the patient with pernicious anemia, it is now generally agreed that liver extract is the treatment of choice, with little indication for the use of folic acid, except in those patients who cannot tolerate liver without severe reactions. There seems to be general agreement that folic acid is of little service in arresting the neurologic changes of this disease. On the other hand, folic acid administered by mouth appears to be the treatment of choice in the megaloblastic anemias that accompany sprue, pellagra, nutritional deficiencies, pregnancy, those of infancy and that syndrome known as achrestic anemia.

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* Delivered December 7, at the mid-year convention of the American Pharmaceutical Manufacturers' Association in the Waldorf-Astoria Hotel, December 6-8, 1948.

** Dean and Professor of Clinical Medicine, The Medical College of Alabama, Birmingham, Alabama.

The discovery of B_{12} by Rickes and his associates and the clinical demonstration of its effectiveness by Randolph West may soon alter the picture in the treatment of the megaloblastic anemias. There is already preliminary evidence that this vitamin is of considerable value in arresting the cord changes of pernicious anemia. I agree with the statement of Castle that the outstanding hematological contribution of the year has been the discovery of this vitamin. If it is shown that this vitamin will arrest cord changes, and that folic acid is an effective hematopoietic agent, then it seems not unlikely that a combination of the two may finally prove to be the treatment of choice in pernicious anemia. For the present, however, the clinician should continue to use liver extract for this purpose.

The great problem of the practicing hematologist is the treatment and management of the patient with leukemia. Leukemia continues to be a progressive and fatal disease, and the life span of the patient with both chronic and acute leukemia continues to be essentially the same as it has been through the years.

The treatment of chronic leukemia has changed very little from our basic dependence upon methods of radiation for its control. Radiation, however, as in other types of tumors, has proved to be relatively unsatisfactory and indeed, when measured by methods used for the control of other diseases is a relatively ineffective palliative agent. New agents are appearing that promise better results in the management of this disease. Among those in use with some degree of success is that known as urethane or ethyl carbamate. This product seems to have a specific action especially with respect to prolongation of life in leukemic mice.

In our hematologic clinic in Birmingham we have now treated nearly sixty patients with urethane over a period of two years, and we have been highly gratified with the clinical results. Patients respond to the administration of this drug with a rather prompt fall of leukocytes to normal levels, disappearance of immature cells from the peripheral blood, and improvement in the bone marrow leukemic picture. Patients have been maintained for many months in a state of satisfactory clinical remission by the use of urethane alone. This makes it possible to defer the use of radiation until a much later date than otherwise would be the case and prolongs the evil day when the patient may become radiation resistant. An occasional patient with chronic leukemia will not respond to urethane at all and the conventional methods of treatment must then be employed.

The outlook for the patient with acute leukemia seems to be better now than it has been in the past, this being brought about by the contributions of Sidney Farber and his associates with respect to the use of aminopterin. We have now treated with aminopterin during the past eight months, a total of 28 patients with acute leukemia. Six of these were practically moribund on admission, and we have recently reported our results in 22, that is, those who received the treatment for two weeks or longer. Of the 22 patients, 13 are dead, and 9 are living. This does not appear to be a satisfactory clinical result as measured on a statistical basis, but 2 of the 4 of the patients treated in the beginning are still living and in a state of satisfactory clinical remission. Certainly aminopterin does not cure acute leukemia, but without doubt it does prolong the life of perhaps 50% of the patients with this disease. It is my belief that those patients whose lives are being prolonged by the use of aminopterin will ultimately succumb to the disease. Most of our patients have died because of hemorrhagic complications. If some means could be devised whereby the thrombocytes could be elevated and hemorrhages controlled, then the ultimate outlook for the patient with acute leukemia would undoubtedly be much better. Perhaps this might eventually be done through the work of Allen and his associates, which I will discuss later. In any event, the demonstration of the usefulness of aminopterin in patients with acute leukemia gives new hope to the management of this hitherto entirely hopeless disease. The greatest promise for the future is that a stronger more specific and more powerful folic acid antagonist may be discovered that would be more effective than aminopterin. One of these in current use is amethopterin. We have not used this in our clinic, but I am advised by Skipper of the Southern Research Institute that it appears more effective than aminopterin in some of his experiments with mouse leukemia.

There seems to be little promise in the control of the leukemic state by use of the radioactive isotopes. Although P_{32}, or radioactive phosphorus, has demonstrated its effectiveness in polycythemia vera, it seems to be no more effective, if as much, in chronic leukemia than the more conventional types of radiation. Plans are well under way now for the construction of a research hospital at Oak Ridge, Tennessee, where extremely short-life isotopes may be clinically applied in the treatment of leukemia and allied disorders. Perhaps

out of this work may be uncovered an agent that will be more effective in the management of this disease.

The use of nitrogen mustard and similar compounds appears to offer some promise in the control of leukemia. At this time its usefulness has been demonstrated in the treatment of Hodgkin's disease, but in the treatment of leukemia of either the chronic or acute type, it seems to offer no advantages over other types of treatment. Its demonstrated effectiveness in Hodgkin's disease offers promise that similar compounds may be brought to light that will be even more effective, not only in Hodgkin's, but in other lymphoblastomas. Altogether, the use of such agents in the treatment of leukemic disorders, agents such as urethane, aminopterin and other folic acid antagonists, radioactive isotopes, nitrogen mustard, etc., comprise the opening of a new chapter in attempts to control these diseases. Much hope may be deduced from the fact that some of them are effective in the various blood diseases and gives promise that newer, more effective, agents may be discovered. It is encouraging that attention is now being centered on this class of compounds rather than our older classic concept of depending upon radiation. In the past we have made the error of referring these therapeutic problems to the radiologist, which has had the effect of stultifying research progress in the management of these diseases.

With respect to the bleeding diseases, no substantial progress has been made in the clinical control of the purpuric disorders. Recent work gives some promise of more effective control, such as that of Allen and his associates at the University of Chicago, who demonstrated an increased heparin content in patients and animals with thrombocytopenic purpura, and who showed further that this could be corrected by the administration of toluidine blue and protamine. Most of us have formerly had the concept that the bleeding from thrombocytopenic purpura and those from coagulation defects are entirely separate and completely unrelated, but this does not seem to be true in view of the work that I have just mentioned.

We have recently had occasion in our clinic to treat two patients who apparently were suffering from hyperheparinemia from unknown cause with toluidine blue and protamine, and the results appear to be quite satisfactory. We have also used toluidine blue in a few of our patients with thrombocytopenic purpura but the results of this are not so clear cut and the use of these agents is questionable in such cases.

It has been demonstrated now that plasma fraction I of Cohn is effective in the control of hemophilia. However, since the only satisfactory source of this fraction is fresh blood plasma, it remains generally unavailable for clinical use. Consequently, in the management of hemophilia, we continue to depend upon transfusions with whole blood and fresh plasma. I personally have the opinion that the use of transfusions by the direct method is superior to the use of blood to which an anticoagulant has been added.

The disease agranulocytosis has almost disappeared, but not entirely so. We see agranulocytosis rarely, and it is now well recognized that it is caused by certain drugs, including the following: amidopyrine, all of the sulfonamide drugs, thiouracil, propythiouracil, gold salts, organic arsenical compounds and perhaps Atabrine, Tridione and Mesantoin, the latter two being in current use for the treatment of epilepsy. The administration of thiouracil has caused a substantial number of cases, but it must not be forgotten that the administration of the less toxic propythiouracil will also cause agranulocytosis as shown by the report of Bartels, who reports ten cases of severe neutropenia in 670 patients receiving this drug at the Lahey Clinic. Aside from the neutropenic states found in many of the primary blood diseases, those that I see more often include those that have developed from the use of sulfonamide drugs, propythiouracil, organic arsenicals, and Tridione. Agranulocytosis is not the serious clinical problem that it once was because the mortality rate has considerably decreased, this being brought about by the widespread use of penicillin for the control of the intercurrent and secondary infections. I have never seen substantial evidence to demonstrate the efficacy of Pentnucleotide and other agents that have been recommended for the control of neutropenia.

Some progress has been made in the treatment of polycythemia vera, the outstanding one being the demonstration that radioactive phosphorus is an effective agent in the control of this disease. Whether or not the use of this agent is more satisfactory than other methods of treatment remains to be seen. It is certainly true that the patient with polycythemia vera can be kept in a state of satisfactory clinical remission over a period of years by the use of simple venesection alone. I am doubtful as to whether the use of radioactive isotopes, other types of radiation, or chemical agents such as acetylphenylhydrazin offer any advanatges over a regime of repeated venesection.

Multiple myeloma is subject to better control now with the use of stilbamidine. Although the value of this drug has not been completely demonstrated, it appears to be a useful agent in the control of the disease. Also, urethane offers considerable promise in the treatment of multiple myeloma. We have recently used large doses of urethane in three cases in our hematological clinic with satisfactory results, with particular reference to the bone marrow picture. Whereas the marrow was literally crowded with approximately 50-90% of multiple myeloma cells in the beginning, the administration of urethane decreases these cells to a relatively insignificant number. Further experience is needed before its usefulness can be evaluated.

Other basis research progress in the field of hematology includes a more general recognition of the role of the spleen in its destructive effects on cells of the blood. There has come to be general recognition of the syndrome generally referred to as hypersplenism which results in a variety of cellular deficiencies in the blood. It is true that there is seen an occasional patient with lowered cell values, an enlarged spleen and a normally functioning bone marrow, which condition can be corrected by removal of the spleen. Hypersplenism results in a variety of clinical syndromes which may include severe anemia, neutropenia, thrombocytopenia, or combinations of these.

Progress in the field of blood transfusions has been greatly augmented by increased knowledge of the various types of Rh factor. The discovery of new factors and red cell antigenic agents has made it possible to give whole blood much more safely than heretofore and is constantly throwing new light on the causation of various hemolytic anemias.

Although continual progress is being made in the field of vitamins, this has not affected the general field of hematology to any considerable degree with the exception of folic acid, ascorbic acid for the capillary fragility in scurvy and related diseases, and vitamin K in hypoprothrombinemia. So far as I can determine vitamins A, B, D, B_2, nicotinic acid, pyridoxine, and pantothenic acid are not effective in the control of any of the hematologic syndromes.

The use of BAL in heavy metal poisoning has had clinical application in the field of hematology in the management of those hematologic states that are caused by poisoning with gold or arsenic.

Considerable advance has been made in some of the technical methods in this field, and this has centered largely around the increasing study of the bone marrow. Studies of the marrow have led to a better concept of the underlying processes of the hematologic states and have contributed to the control and management of many hematologic disorders. Although from a pathological standpoint much more information can be derived from biopsied specimens of marrow, this is an impractical procedure in clinical hematology and we must be content to utilize aspirated material even with its shortcomings. The utilization of aspirated material of course has the major disadvantage that one is dealing with cytological material without an organized pattern. Consequently, reliable interpretation and conclusions are much more difficult than if an architectural pattern were present.

Other work in hematology that appears important includes the observations of Ashby, who has found that the life span of the red cell is about 120 days. Certainly the work of Knisely and his associates on sludged blood may prove to be of great fundamental importance. Some observations have been made on the use of massive blood transfusions in such diseases as leukemia and erythroblastosis but these procedures may be dangerous because of liver damage.

The outstanding problems in the field of hematology that require solution include the nature of the leukopoietic factor as well as the thrombocytopoietic factor. During the past twenty years a great deal of progress has been made in the evolution of knowledge concerning the erythropoietic factor as shown by the advent of liver extract, folic acid and vitamin B_{12}, but surprisingly enough hardly any knowledge has accumulated with respect to the other cell factors.

From the standpoint of therapy the outstanding problem is leukemia, and it seems unlikely that this will ever be solved as a separate entity because, of course, it is one of the malignant diseases.

Another disease that is troublesome for the hematologist is the one known as aplastic or refractory anemia and no progress has been made in the control of this disease.

I am sure that the ultimate solutions to these problems will come from the contributions of the physicist, chemist and biologist because, after all, those are the sources of all major medical advances.

In this discussion I have not used the names of the various contributors responsible for advances, but a bibliography is appended.

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THE PRESENT STATUS OF POLYMYXIN, CHLOROMYCETIN AND AUREOMYCIN: EXPERIMENTAL AND CLINICAL *

By Perrin H. Long, M. D.**

DURING the past eighteen months, three new antibiotic agents, polymyxin chloromycetin and aureomycin have been described. It will be my purpose today to discuss briefly certain observations which have been made by my colleagues, myself, and others, on the antibacterial or bacteriostatic activity, the pharmacology and toxicity, the comparative effectiveness in experimental infections, and the potential clinical uses and value of these three compounds.

Bactericidal and Bacteriostatic Activity

It can be said that from the point of view of antibacterial activity, polymyxin (aerosporin) *in vitro* is definitely more effective than is streptomycin against certain gram negative bacteria. In our experience polymyxin has from two to eighty times the activity of streptomycin against susceptible bacteria. Furthermore, the activity of polymyxin is primarily bactericidal in the concentrations used, while that of streptomycin is bacteriostatic. Another point of interest is that we have been unable to produce resistant organisms by exposure to polymyxin over long periods of time. Chloromycetin and aureomycin exert bacteriostatic effects on certain gram positive and gram negative bacteria *in vitro*. In testing these effects, the comparison for gram positive organisms has been made with penicillin, while streptomycin has been used for comparison in the instance of the gram negative organisms. Under the conditions of the tests, aureomycin was found to be from four to sixteen times as active as was chloromycetin against streptococci, pneumococci and staphylococci, and from ten to eighty times less effective than penicillin ex-

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cept in the instance of streptococci belonging to Group D in Lancefield's classification. When gram negative organisms were tested, the bacteriostatic activity of aureomycin and chloromycetin were comparable, but generally less than the antibacterial activity of polymyxin. The exceptions to this are the relative effectiveness of chloromycetin against strains of *P. vulgaris,* and the almost total lack of activity of chloromycetin and aureomycin against strains of *Ps. aeruginosa.* Aureomycin has also been tested against five strains of organisms belonging to the Brucella group and has been an effective bacteriostatic agent in concentrations of 0.75 micrograms per ml. or less. Other investigators have reported that polymyxin has an antibacterial effect against *A. aerogenes, E. typhosa, E. coli, K. pneumoniae, P. multocida, S. gallinarum, S. pullorum* and *S. flexner;* and that chloromycetin has a bacteriostatic action against *S. schottmulleri, Shig. paradysenteriae* (Sonne), *B. mycoides, Borrelia recurrentis, Br. abortus, Br. suis, Br. melitensis, E. typhosa, H. pertussis, P. tularense,* certain strains of *Mycobacterium tuberculosis, var. hominis,* and certain yeasts and filamentous fungi.

Experimental Toxicity

Polymyxin is moderately toxic for white mice, the LD 50 being 250 to 300 milligrams per kilogram when given by a single subcutaneous injection. Because of its relative insolubility, it is difficult to determine the LD 50 of chloromycetin for mice. However, it has been reported that the LD 50 of this compound in propylene glycol is 245 milligrams per kilogram when administered to white mice by the intravenous route. For aureomycin, the LD 50 for white mice was found to be 3500 milligrams per kilogram when this antibiotic was administered by the subcutaneous route. In larger animals such as dogs, 10 milligrams of polymyxin D per kilogram given twice a day for 7 days by the intramuscular route was well tolerated; with chloromycetin, dogs reciving from 72 to 80 milligrams per kilogram per day by the intramuscular route for 38 doses (5 days a week) developed varying degrees of anemia during the period of the test, while dogs reciving 40 milligrams per kilogram per day of aureomycin for 9 days by the intramuscular route showed signs of anorexia and loss of weight. Because the hydrochloride of aureomycin which is quite acid, was used in these tests, varying degrees

of local necrosis were noted. Neither polymyxin, nor aureomycin, nor chloromycetin produced any significant changes in the white blood cell counts, blood non-protein nitrogen, blood sugar or liver function tests. All samples of polymyxin tested to date have produced albumin, casts, white and red blood cells in the urine of rats which had received 20 milligrams per kilogram of polymyxin daily by the intravenous route. Histological examination of the kidneys of such rats showed definite evidence of lower nephron damage. Certain specimens of polymyxin have produced symptoms and signs of histamine shock when injected into rats by the intramuscular route. It is probable that these reactions result from impurities in the material under test.

Pharmacology

Polymyxin passes readily into the blood stream following its intramuscular injection into dogs. Ninety minutes after dogs had received single intramuscular doses of 5 or 10 milligrams per kilogram, concentrations of 2.5 and 5.0 micrograms of polymyxin per ml. were recorded. Detectable amounts of the antibiotic were still present in the serum at three and one-half hours. When dogs were given 5 or 10 milligrams of the compound per kilogram twice daily for 7 days, concentrations of from 10 to 20 milligrams of polymyxin per ml. of serum were noted. No polymyxin was detected in the spinal fluid of dogs in whose serum high concentrations of polymyxin were present. When polymyxin was administered to human beings in divided doses by the intramuscular route at intervals of 3 hours in amounts not to exceed a total daily dose of 3 milligrams per kilogram of body weight, concentrations of 0.6 to 1.3 micrograms of the antibiotic per ml. were noted in the serum after 24 hours of therapy. Detectable amounts of the antibiotic were present in the urine of these patients. To date, it has not been found in the spinal fluid of patients suffering from purulent meningitis and treated with this antibiotic.

Aureomycin deteriorates quite rapidly when placed in solution. It is also bound by the proteins of blood serum in varying degrees. Hence, when biological testing against a strain of a susceptible microorganism is used for determining concentrations of this antibiotic in body fluids, the method is fraught with error. The same is probably true when bacteriostatic tests are done. The figures obtained do not represent true values but rather qualitative instead of quanti-

tative results. With this in mind, the following data are presented. When dogs and rabbits were injected with single doses of 20 or 40 milligrams of aureomycin by the intramuscular route, concentrations of slightly over 1 microgram per ml. of the antibiotic were noted in the serum within 1 hour but not after that time. In a dog receiving 20 milligrams of aureomycin per kilogram of body weight twice a day for 10 days, the antibiotic could be detected in the serum up until two and one-half hours after each injection. While the antibiotic was not observed in the spinal fluid, it did appear in quantity in the urine. When aureomycin was administered orally to human beings in doses of 500 milligrams twice a day and 40 milligrams every 6 hours by injection, concentrations of from 0.6 to 2.4 micrograms per ml. of the antibiotic were observed in the serum 1 hour after the injection was given. The antibiotic produced a greenish yellow discoloration of the urine, in which concentrations of from 50 to 80 micrograms per ml. were observed.

Chloromycetin appears promptly in the blood after a single oral ingestion or intramuscular injection of this antibiotic. It also would appear that it is excreted fairly rapidly in the urine in which its recovery (as measured by biological tests) is fairly high. In experiments in which chloromycetin was administered to dogs over a period of 24 days by the oral or intramuscular routes, concentrations of from 1 to 29 micrograms per ml. of serum of chloromycetin were noted 2 hours after treatment, and concentrations of 1 to 2 micrograms per ml. of serum, 18 hours after treatment. Concentrations of from 36 to 406 micrograms per ml. were noted in the urine of these dogs. It was also determined that chloromycetin was bound to the proteins of the serum to the extent of about 45 per cent. In patients ill with typhoid fever, and treated with initial daily doses of between 4 and 5 grams of chloromycetin, concentrations of from 40 to 80 micrograms were noted in the blood within the first 24 hours of treatment. It was also noted that the concentration of chloromycetin in the spinal fluid was approximately half that noted in the blood.

Treatment of Experimental Infections

Polymyxin has been shown to be an effective chemotherapeutic agent in the treatment of experimental infections in mice produced by *K. pneumoniae*, Type A (Friedlander bacillus), *H. influenzae*,

P. multocida, and *Shig. gallinarum*. In our hands it appears to be from 5 to 10 times more effective in the control of infections produced in mice by *K. pneumoniae* and *H. influenzae* than is streptomycin.

Chloromycetin has been shown to have a chemotherapeutic effect in experimental rickettsial infections, *K. pneumoniae*, Type A, *Shigella paradysenteriae*, Sonne, *D. pneumoniae*, *Strep. hemolyticus* and *Strep. viridans*, certain viruses of the psittacosis group. Cox demonstrated that aureomycin is an effective chemotherapeutic agent in the treatment of experimental infections produced by various types of rickettsia. SubbaRow and his co-workers have shown that this antibiotic controlled experimental infections in mice produced by hemolytic streptococci, pneumococci or *K. pneumoniae*, Type A.

In our own laboratory in which tests were made of the comparative therapeutic effects of chloromycetin, aureomycin, polymyxin and penicillin in certain experimental infections in mice, the following results have been obtained. In experimental infections in mice produced by the injection intraperitoneally of 10,000 M. L. D. of *K. pneumoniae*, Type A, aureomycin and chloromycetin showed essentially equal therapeutic activity. Both were about a hundred times less effective at the dosage levels employed than was polymyxin, and about ten times less effective than streptomycin. In the treatment of experimental infections in mice produced by the intraperitoneal injection of 10,000 M. L. D. of *Strep. hemolyticus* (strain C203), aureomycin appeared to be about twenty-five times more effective than chloromycetin, and about ten times less effective than was crystalline penicillin G. When mice was infected with 10,000 M. L. D. of *D. pneumoniae*, Type I (strain SVI), and then treated, aureomycin was more than forty times as effective as a therapeutic agent than was chloromycetin, and about five times less effective than was crystalline penicillin G. In these tests only an approximate comparison could be made between aureomycin and chloromycetin because of the relative insolubility of the latter compound. It should be noted that in making all of these comparisons of therapeutic effectiveness, the mice were treated by the subcutaneous route immediately, at 5 hours and then at 23 hours after they had been infected. They were observed for 6 days after therapy had been discontinued.

Treatment of Infections in Human Beings

There can be no doubting of the therapeutic effectiveness of polymyxin for the treatment of local and systemic infections produced in human beings by certain gram negative bacilli. Outstanding among the infections which have responded to treatment with this antibiotic have been those due to *Ps. aeruginosa, K. pneumoniae, H. pertussis, H. influenzae* Type B, and *E. coli.* In severe instances of such infections which were treated by the intramuscular injection of polymyxin at 3 hour intervals, the results frequently have been very satisfactory. In these patients the total daily dose of polymyxin has been based upon 3 to 5 milligrams of the antibiotic per kilogram of body weight, this being split into 8 equal doses and given in a special buffer solution (pH 7.4) at intervals of 3 hours. It is indeed unfortunate that the toxicity (as will be described later) of the various specimens of polymyxin which have been tested to date, is such as to preclude the general use of this antibiotic.

Chloromycetin has been shown to be a highly effective therapeutic agent in the treatment of epidemic typhus, scrub typhus, Rocky Mountain spotted fever, Eastern variety, and typhoid fever. Payne and his associates have reported that chloromycetin in doses of 10 milligrams per kilogram of body weight per day given by the intravenous route, or 15 milligrams per kilogram of body weight per day given by the oral route for a period of 3 days, was effective in the treatment of severe epidemic typhus fever. Smadel et al. have described the treatment of scrub typhus with this antibiotic. In 25 patients suffering from this disease, the administration of chloromycetin in varying doses brought about a prompt cure. Doses as small as 6.0 grams of chloromycetin given for *1 day* produced satisfactory responses. Pincoffs and his co-workers have tested the effects of chloromycetin in 15 patients ill with Rocky Mountain spotted fever, Eastern variety. Here again, excellent results were obtained in all patients who were treated. Finally, Woodward, Smadel, Ley, Green and Manikas have found that chloromycetin administered by mouth in initial doses of 50 milligrams per kilogram and continuing doses of 0.25 gram every 2 hours until the temperature was normal, and then the same dose every 3 or 4 hours for the ensuing 5 days, exerted a specific therapeutic effect in 10 patients ill with early typhoid fever, all of whom had a blood culture positive for *E. typhosa* before treatment was started. The average time in

which the temperature returned to normal in these 10 patients was 3.5 days. Chloromycetin has been in short supply. As a result we have had no clinical experience with this antibiotic. It would seem very clear, however, that it is an extremely effective antibiotic for the treatment of rickettsial diseases, its use in typhoid fever seems established, and from experimental observations *in vitro* and *in vivo* it is likely that chloromycetin will prove to be an effective chemotherapeutic agent in infections produced by certain gram negative organisms and viral agents.

We have reported that aureomycin appeared to be an effective chemotherapeutic agent for the treatment of Rocky Mountain spotted fever, Eastern variety, urinary tract infection produced by *E. coli*, acute brucellosis, and typhoid fever. Recently, Braley and Sanders have described the effectiveness of this antibiotic in the treatment of certain bacterial and viral infections of the eye. Wright and his co-workers have demonstrated that this antibiotic has a therapeutic effect in lymphogranuloma venereum and granuloma inguinale. Finland et al. have stated that aureomycin appears to have a beneficial effect in coccal infections and in certain infections of the urinary tract.

Today our group wishes to report on further clinical experiences with aureomycin. Sixteen patients ill with Rocky Mountain spotted fever, Eastern variety, of whom 13 were proven by serological methods, have been treated with aureomycin. The details of this clinical test are being described by Ross et al. Suffice it to say that the results obtained were excellent. The average day of treatment in these patients was 4.5. The temperature returned to normal in an average of 2.3 days. There were no complications. The average period of hospital stay was 8 days. One patient severely ill with Brill's disease has been treated with prompt and excellent results, as has also one patient suffering from Q fever.

Thirteen patients, who by all available methods of exclusion, have had the diagnosis of primary atypical pneumonia made in their illness, have been treated with aureomycin with excellent results. In 9 the temperature was normal in 24 hours, in 2 within 48 hours, while in one patient 72 hours passed before this desirable state was reached. All experienced prompt symptomatic relief and the pneumonic processes in their lungs cleared rapidly after treatment

was initiated. The details of this clinical test are being reported by Schoenbach and Bryer.

Five patients ill with acute or subacute brucellosis, in all of whom positive blood cultures were obtained, have been treated with aureomycin. In 3 of these patients the infection was due to *Br. suis*, while in the other 2, *Br. abortus* was recovered from their blood. All had typical symptoms of the disease and had enlarged spleens. The titer of antibody for their specific strain of the Brucella group was high in the serum of each patient. One had failed to be cured by previous treatment with sulfadiazine, streptomcyin and sulfadiazine and polymyxin, while another had had an ineffectual course of streptomycin and sulfadiazine. In all 5 patients there was a dramatic clinical response to the administration of aureomycin, with the temperature falling to normal within 72 hours and with a progressive remission of all symptoms and signs. Treatment was carried out over a 14 day period. These patients have been followed from 2 to 6 months. All have gained weight consistently, and none has shown any symptoms or signs of a return of their disease.

Five patients suffering from various forms of tuberculosis have been treated. In 2, suffering from tuberculosis meningitis, the antibiotic was not effective. In a 12 year old Negro child who had three scrofulous sinuses in her neck, from each of which tubercle bacilli were recovered in culture, the administration of aureomycin for one month resulted in the closure of all sinuses a week after treatment had been started, and after 3 months, there has been no recurrence of the disease. The fourth patient was suffering from advanced tuberculosis of the renal tract with marked involvement of the bladder. One kidney had been removed because of the infection. This man has been under treatment for 2 months and has experienced a marked remission of the symptoms and signs of his disease. He is still under treatment and his progress will be reported subsequently. A fifth patient ill with cavitating tuberculosis was treated for 2 weeks with aureomycin without evidence of clinical improvement. At the time of this writing, it must be made clear that no claims are being made for the therapeutic use of aureomycin in tuberculosis. We are just reporting our observations.

Five cases of typhoid fever have been treated with aureomycin. While all have recovered and their blood and stool cultures became negative soon after antibiotic therapy had been instituted, the results

as far as the decline in the fever and the general improvement of the patient were equivocal and might well have been due to chance. Chloromycetin would appear to be definitely superior to aureomycin for the treatment of this disease.

Eight patients suffering from serious and complicated infections of their urinary tracts have been treated with aureomycin. All had received sulfonamides, penicillin or streptomycin previously. All had gross anatomical or other abnormalities of their urinary tracts. The infecting organisms were *E. coli, A. aerogenes,* or *Strep. fecalis* or a mixture of two or more of these micro-organisms. The immediate effects from therapy were good in 7 and fair in one of these patients. It remains to be seen what the long time results will be. Aureomycin is ineffective in urinary tract infections in which *Ps. aeruginosa* or *P. vulgaris* are the etiological agents.

Eight patients ill with moderate to severe infections produced by *Staph. aureus hemolyticus,* in 2 of whom a staphylococcal bacteremia was present, have been treated with aureomycin. In several of these patients antecedent therapy with sulfadiazine and or penicillin had been unsuccessful. In 7 of the 8 patients prompt and satisfactory responses to therapy were noted. In the eighth, an infant whose initial infection was a staphylococcal pyodermia, extensive signs of pulmonary involvement were present despite continuous therapy with penicillin for a period of more than 2 months. When treatment with aureomycin was initiated, the pulmonary signs cleared rapidly except for one small area. After 2 weeks of therapy with aureomycin, material for culture was obtained from this area by bronchosopic examination, and a strain of *Staph. aureus hemolyticus* which was resistant to more than 10 micrograms of aueromycin per ml., was isolated. This patient must be counted as a failure.

Whenever a new antibiotic is being tested clinically, a number of patients with curious infections for which there is no experimental evidence for the use of the antibiotic must be treated if only to maintain harmony in the society of physicians. Certain of these patients whom we will place in the category of "miscellaneous infections" will be discussed. Among the patients in this group for whom there was experimental evidence attesting to the possible value of aureomycin in the treatment of clinical disease were the following. One patient ill with meningitis produced by *Strep. fecalis,* was promptly cured by the administration of aureomycin. One patient ill with

pneumococcal meningitis produced by *D. pneumoniae* Type 6, had been treated with sulfadiazine, penicillin and streptomycin with the result that the infecting organism had become resistant to all three therapeutic agents. Cultures of the spinal fluid were abundantly positive for *D. pneumoniae* before therapy with aureomycin was initiated. Recovery was prompt after this antibiotic had been administered. One patient suffering from subacute bacterial endocarditis due to *Strep. fecalis* had been treated with crystalline penicillin G with very satisfactory results until fever, hives and arthritic symptoms and signs developed as a toxic reaction to penicillin therapy. Penicillin was discontinued and the blood culture became positive again for *Strep. fecalis.* Treatment with aureomycin was instituted in doses of 1.8 to 3.2 grams per day and continued for 11 weeks. While final judgment cannot be passed, it can be said that the initial results of therapy were excellent, and to date there has not been a recrudescence of the disease. Two patients who had brain abscesses, one due to *Staph. aureus hemolyticus* and the other to *E. coli,* have been treated with satisfactory results. Two patients ill with peritonitis, in one of whom the infection was produced by *E. coli* and *Strep. fecalis,* while in the other, infection was due to *Strep. fecalis,* have been successfully treated with aureomycin. In both instances the response to therapy was prompt, and in both aureomycin was used as an adjunct to surgical therapy. Two patients ill with whooping cough did not respond to treatment with aureomycin. One patient each with polio-encephalitis, noma, erythema multiforme, and pancreatic necrosis with secondary infection have been treated without results.

Up to the present time, the method of choice for the use of aureomycin is to give it by mouth. A satisfactory preparation for general intravenous use has not been developed so far. The antibiotic as supplied is a hydrochloride salt and when this is administered intramuscularly, it produces pain due to the acidity of the product. This has militated against its use by this route. It is too early in the history of aureomycin to establish accurate dosage schedules for the administration of this antibiotic. It is likely that the dosage schedules which we recommend at this time will eventually be proven to have been excessive. However, they have been effective. In severely ill patients who are being treated orally, the total daily dose of aureomycin should be based on 60 milligrams per kilogram

of body weight per day. Initial "priming" doses equivalent to one-sixth of the total daily dose should be given to seriously ill patients at hourly intervals for 3 doses. Then one-sixth of the estimated dose should be given at 4 hour intervals until the temperature has been normal for 24 hours. At this time the basis for the total daily dose should be reduced by one-half or to 30 milligrams per kilogram of body weight. This is divided into 4 parts and is given at 6 hour intervals until the infection is eliminated. In moderately severe infections the total daily dose should be based on 30 milligrams per kilogram of body weight, this to be divided into 4 or 6 equal parts and given at 4 or 6 hour intervals until the infection is under control. As approved parental derivatives of aureomycin are not available, their use will not be discussed.

Clinical Toxicity

Polymyxin, being a polypeptide or a mixture of polypeptides, should not produce toxic reactions as the result of the sensitization of the patient to the antibiotic. To date this has been true as far as our experience has gone. All specimens of this antibiotic which we have tested have produced varying degrees of renal tubular dysfunction. In the mildest form it appears as a fixation of the specific gravity of the urine, while in severe forms, oliguria with albumin, casts, red blood cells and white cells in the urine, an elevated non-protein nitrogen, and depressed renal function may occur. These latter reactions sometime become very disturbing and it is because of them that the general use of polymyxin seems contra-indicated. Histamine like reactions, hyperesthesias and fever have been noted in the course of polymyxin therapy, but these reactions would appear to be due to impurities in the specimens of polymyxin which were being used, rather than to the antibiotic itself.

Neither aureomycin nor chloromycetin have shown significant evidence of clinical toxicity up to the present time. This is extremely interesting, because despite the fact that both of these products are derived from members of the family of streptomyces, reports of sensitization or other toxic reactions have not been made, and this in face of the fact that several hundred patients have been treated with these antibiotics. Some nausea has been reported by patients receiving aureomycin, but this can be easily controlled by the administration of preparations containing aluminum hydroxide. Oc-

casionally, looseness of the bowels is associated with aureomycin therapy.

Conclusions

I. Polymyxin is an effective antibiotic for the treatment of severe infections produced by *Ps. aeruginosa, H. pertussis, H. influenzae, E. coli* and *A. aerogenes.* Its toxicity to date precludes its general use in infections susceptible to its therapeutic effects.

II. Chloromycetin has been demonstrated to be an effective antibiotic agent for the treatment of rickettsial diseases and typhoid fever. It will undoubtedly prove effective in the treatment of other infections produced by *Ps. aeruginosa, H. pertussis, H. influenzae,* viral agents.

III. Aureomycin has been shown to be an active antibiotic agent against rickettsial diseases, primary atypical pneumonia, acute brucellosis, staphylococcal infections, urinary tract infections produced by *E. coli, A. aerogenes* and *Strep. fecalis,* certain eye infections, pneumococcal and streptococcal infections, and certain infections produced by viral agents. Its clinical use in forms of extra pulmonary tuberculosis is in the highly experimental stage. It is not recommended in typhoid fever and it seems to be ineffective in whooping cough.

IV. To date, neither chloromycetin nor aueromycin have shown significant signs of toxicity.

BASIC RESEARCH PROGRESS IN THE FIELD OF HEART DISEASES*

By Arthur C. DeGraff, M. D.

RESEARCH in diseases of the heart has progressed so rapidly and along so many different lines that it will be impossible in the time allotted to me to cover the whole field. As a matter of fact, all I can do is to mention briefly what is going on in a few selected branches of the subject. I will discuss some of the important work that is being done in the treatment of congestive heart failure, in hypertension, in rheumatic fever, and in the treatment of coronary artery thrombosis. Since this audience is chiefly interested in treatment, I will stress research which is concerned with treatment rather than with diagnosis.

Congestive Heart Failure

In congestive heart failure the role of the kidney in the mechanism of edema is now fairly well understood. It is well established now that in spite of the fact that the renal blood flow is reduced in the presence of congestive heart failure, sometimes to as low a level as one-fifth normal, tubular reabsorption of sodium is normal. That is why there is sodium retention in congestive heart failure leading to the production of edema. Using radioactive sodium, it has been found by Burch and his associates that a normal individual on an unrestricted salt-intake would excrete on the average ninety times as much sodium as would the patient in congestive heart failure. Burch has also shown that the retention of sodium in cardiacs is directly related to the degree of failure. Whereas the normal person excretes half of the total body sodium in about fifteen days, the patient in congestive heart failure requires about forty days to excrete the same relative amount. The mercurial diuretics by preventing the reabsorption of sodium are extremely valuable in the treatment of congestive heart failure. Because of the theophylline contained in

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chemical combination with the commonly used mercurial diuretics, tissue necrosis at the site of injection is rare, and even when the drugs are injected intramuscularly absorption is rapid and almost complete. Storage of mercury does not occur unless there is kidney damage or the mercurials are given at too frequent intervals. These drugs are so efficient in removing sodium from the body that danger of excessive sodium depletion and other disturbances in electrolyte balance exists if they are given every day as is suggested by one enthusiastic investigator. Sudden death by ventricular fibrillation, although rare, can occur when a mercurial diuretic is injected intravenously. A new mercurial diuretic in which a sulfhydryl radical replaces theophylline appears to have removed even this danger in that this diuretic can be given intravenously in large doses without danger of ventricular fibrillation. This diuretic also appears to be less irritating at the site of injection, so that in many cases it can even be used subcutaneously.

In the field of digitalis therapy, more studies on the cardiac glycosides are appearing in the literature every day. It is apparent now that the glycosides vary considerably one from the other in speed of action and duration of effect. The length of time the toxic manifestation may be present also varies considerably. The shorter acting glycosides such as ouabain and lanatoside C are extremely valuable for intravenous medication where prompt action is desired, since the beginning effect of these drugs is within a few minutes. Many adverse reports are beginning to appear in the literature on digitoxin, which has been forced onto the medical profession by many drug houses with the same high-pressure technique used in cigarette advertising. This glycoside now is shown by many observers to have such a long period of dissipation and such prolonged toxicity that it is difficult for the average physician to use. Master, Flaxman, Stewart and others have recently commented on the difficulties and dangers in using digitoxin in the treatment of cardiac patients.

At the present time the most satisfactory glycosides for initial oral digitalization and maintenance are digoxin and gitalin. A synthetic cardiac glycoside has not yet been produced, but careful pharmacological studies on many cardiotonic substances and a correlation of these studies with chemical structure will, I am sure, eventually produce a series of synthetic substances which will replace the glycosides now derived from digitalis and other crude drugs.

Hypertension

Much energy and money is being expended in attempts to solve the problem of hypertension. As yet, however, although many interesting features of clinical hypertension have been brought to light, the final solution is not yet at hand. It might be helpful to review some of the problems connected with various forms of treatment.

(a) Marked sodium restriction in the diet, such as the rice diet of Kempner, does appear to cause the blood pressure to fall and produce a relief of symptoms in a fair number of patients. Some of the results in individual patients as reported by Kempner are actually startling. Kempner himself admits that he doesn't know the mechanism by which these beneficial results are obtained. It is generally believed by others that the good results are due to the low sodium diet, yet most physiological studies indicate that kidneys of the average hypertensive patient handle sodium normally and no retention of sodium occurs in hypertension unless there is associated congestive heart failure.

(b) It is suggested by some that psychotherapy will cause the blood pressure to fall in many cases and that results obtained with other forms of therapy are in fact due to suggestion and psychotherapy. Although psychotherapy is undoubtedly an important adjunct in the treatment of hypertension and may in some cases be the only treatment necessary, Binger, himself a psychiatrist, has warned that psychotherapy is at best only supplementary therapy.

(c) Surgical treatment (dorso-lumbar sympathectomy) has afforded relief in some instances, but the dangers of this operation and the frequency of poor results has caused it to be limited now to only a few selected cases. Fishberg has recently stated that he would advise less than 3 per cent of hypertensive patients to have the operation performed. The real difficulty with dorso-lumbar sympathectomy is the inability to determine in advance which patients are likely to be benefited and which ones might be made worse.

(d) In the field of drug therapy many substances have been found that will reduce blood pressure. However, because of the toxic nature of many of these substances, or undesirable side actions, or the short duration of effect, the studies so far have been largely of an experimental nature. For instance, tetra ethyl ammonium salts by blocking the reactivity of the vascular system to pressor agents have become useful in the study of the hypertensive state. Many

substances have recently been found to depress the blood pressure by central action. For instance, pentaquine used in the treatment of malaria has been found by Freas and Wilkins as well as by Moe and Seevers to reduce blood pressure, apparently by depressing sympathetic nervous reflexes. Dihydroergocornine by action on the higher autonomic centers in the medulla and hypothalamus will reduce blood pressure. It is the only known ergot alkaloid, according to Goetz, with purely sympathicolytic effect on the peripheral vessels in man, and the direct vasoconstrictor action on the peripheral vessels common to other ergot alkaloids is absent. The dose required is a rather critical one and varies from patient to patient. Small doses have a definite depressor effect, whereas large doses cause a rise in blood pressure associated with side effects such as nausea and vomiting. Hence this drug is rather difficult to use in the treatment of patients.

Recently a very old drug, namely, veratrum viride has been revived for the treatment of hypertension by Freis and Stanton. Their study was possible only because a method has now been devised for standardizing veratrum viride by means of "Craw" units. Forty patients were studied, using the drug orally. A hypertensive effect occurred in 1-2 hours, the maximum effect in 4-6 hours and disappearance of effect in 14 hours.

A fall in blood pressure is apparently associated with peripheral vasodilation, not depression in cardiac output. Apparently the mechanism is as follows:

> "A reflex fall in blood pressure and heart rate following injection of veratridine originates from the afferent vagus nerve endings in the myocardium of the left ventricle and in the lungs. These ordinarly send out bursts of activity with each heart beat but fire continuously with veratrum alkaloids."

Rheumatic Fever

I would like to make brief statement about rheumatic fever research. The relationship between Group A, beta hemolytic streptococcus infections of the throat and the subsequent occurrence of rheumatic fever seems to be well established. Prevention of rheumatic fever, therefore, concerns itself largely with the prevention of streptococcus infections of the throat. Several years ago studies in a number of places demonstrated that the daily oral administra-

tion of sulfonamides would prevent streptococcus throat infections. However, the experience of the armed forces indicated that Group A streptococci of types 17 and 19 were sulfonamide-resistant and there was no protection if these strains were involved. Recent studies with penicillin tablets given by mouth in doses of 100,000 units a day suggest that all Group A beta hemolytic streptococcus infections might be prevented. No resistant strains have so far been encountered and it is possible, therefore, that this method of prophylaxis will replace the use of sulfonamides. Protection is afforded only against beta hemolytic streptococci, however, and not alpha, streptococci. One child under treatment for several months developed subacute bacterial endocarditis and responded only upon large intramuscular injections of penicillin. Incidentally, excellent results are now reported on the use of penicillin in subacute bacterial endocarditis. The dosages now recommended are high. Two to five million units a day continued for at least for weeks after the temperature is down are commonly given. In some cases doses up to 20,000,000 units daily have been reported. The percentage of cures seems higher the larger the dosages used.

Arteriosclerosis and Coronary Artery Disease

It wasn't very long ago that arteriosclerosis was considered an inevitable event of aging for which nothing could be done. The increasing incidence of arteriosclerosis, particularly coronary artery sclerosis in young people, indicates quite clearly that arteriosclerosis is a disease quite apart from general aging of tissues. Yater and his associates have recently analyzed the records of 866 cases of coronary artery thrombosis occurring in young men (18-39) while they were in the armed forces. In the 450 deaths in this series all showed advanced arteriosclerosis of the coronary arteries. Yater's careful analysis of the factors involved suggests heredity and hypertension as the most important.

The role of cholesterol in the development of arteriosclerosis is much debated at this time. It is known that in diseases where high blood cholesterol is found, such as uncontrolled diabetes and myxedema, there is advanced arteriosclerosis. Also, there are studies which suggest high cholesterol-intake in the diet favors the development of arteriosclerosis. On the other hand, there is considerable evidence that cholesterol found in the blood of normal in-

dividuals is endogenous in origin, quite independent of the diet. Perhaps some endocrine or vitamin factors determine whether or not a high cholesterol-intake in the diet will favor the development of a high cholesterol blood level and the development or acceleration of arteriosclerosis. It is already known that thyroid deficiency favors a high blood cholesterol. This has also been suggested for vitamin E deficiency.

Whatever may be the factors involved, however, coronary arteriosclerosis is very common, and its complication, coronary artery thrombosis, takes a large toll in lives and disability. The death toll from coronary thrombosis has been materially reduced by the use of anticoagulant therapy. Prior to 1946 there were a few isolated reports which suggested that either heparin or dicoumarol or both could favorably influence the course of coronary artery/artery thrombosis. In 1946 a committee for the evaluation of anticoagulants in the treatment of coronary thrombosis with myocardial infarction was instructed by the American Heart Association to gather data on 1,000 cases. This study is now complete. Sixteen hospitals in various parts of the country cooperated and records were assembled and analyzed at a central office. Every precaution was taken in advance to make the study on a sound statistical basis. As a matter of fact, well known statisticians acted as advisors throughout the entire study.

The patients in the treated group received heparin in some cases for 48 hours. Dicoumarol, 200 to 300 mg., daily was given immediately and continued until the prothrombin time was 30 seconds. The daily dose of dicoumarol was then adjusted to keep the prothrombin time between 30 and 35 seconds. The patients in the control group were given the conventional treatment without anticoagulants. The results are striking. Although 24 per cent of patients in the control group died, only 15 per cent of patients treated with anticoagulants died. Another significant finding in this study was low incidence of thromboembolic complications in the treated group. Hemorrhagic phenomena were rare and when present were not serious. The committee recommended that anticoagulant therapy be used in all cases of coronary artery thrombosis with myocardial infarction, providing there are facilities for adequate laboratory and clinical control and there are no definite contra-indications such as gastric ulcer or hemorrhagic conditions.

SELECTED ABSTRACTS

Solution G, a Urinary Calculi Solvent. C. J. M. Wozencroft. *Pharm. J. 161:*111 (1948). Urologists have long been striving to develop some means of removing urinary stones without having to resort to surgery. The author reviews some of the developments in the field of solvents leading up to the formulation of Solution G. The primary drawback of previous solvents has been their irritation of tissue. Irritability has been reduced considerably in Solution G. It has also been found that this solution has some bactericidal value. The solution is only applicable to phosphatic stone, composed of calcium phosphate with or without calcium carbonate and/or magnesium ammonium phosphate.

Solution G has the formula:

Citric Acid	32.3 Gm.
Magnesium Oxide (Anhyd.)	3.8 Gm.
Sodium Carbonate (Anhyd.)	4.4 Gm.
Distilled Water q. s.	ad. 1000.0 cc.

The pH of this solution is 4. Both of the salts must be anhydrous as a decrease in the relative amount of these salts will increase the acidity and thus increase the irritability. The citric acid is dissolved in 600 cc. of distilled water, the magnesium oxide added, and then the sodium carbonate in small portions. When the effervescence has ceased the solution is boiled to expel the excess carbon dioxide. After cooling the solution is adjusted to volume, filtered and sterilized in the autoclave for 30 minutes at 10 lb. pressure. Overheating may char the solution. The solution is stable under normal storage conditions.

Podophyllin Resin Used in the Treatment of Condylomata Acuminata. W. N. New and W. C. Marsh. *U. S. Nav. Med. Bull. 48:*831 (1948). Seventy-five cases of condylomata acuminata were treated with applications of 25 per cent podophyllin in compound benzoin tincture. Complete eradication of all lesions was obtained with 78 per cent of the lesions disappearing after the first application. The remainder required 2 or more applications but only

2 cases required more than 3 applications of the preparation. The authors pointed out that the application must be made with care. The digitations of the verrucae must be spread in order to permit penetration but that care must be taken not to penetrate to the base as edema and much discomfort would follow. Opposing surfaces must be kept separated until the preparation has thoroughly dried. There is a tendency for repeated applications to produce marked local sensitivity.

Compound benzoin tincture was selected as the vehicle because the 77 per cent alcohol content keeps the podophyllin in solution and the benzoin, storax, aloe, and tolu causes the preparation to adhere to the surfaces of the lesions.

Podophyllin apparently acts directly on the epithelial cells. Histopathological examination reveals degeneration accompanied by the production of bizarre cells now called "podophyllin cells."

The misnomer venereal warts is often applied to condylomata lesions but they are definitely not of venereal origin. The lesion often resembles a cockscomb or red-cauliflower mass. It is bright red, moist, highly vascular, sessile or pedunculated and often friable.

Use of Curare in Anesthesia. C. W. Reynolds. *U. S. Nav. Med. Bull. 48:668* (1948). Curare was used throughout the operative period to obtain muscular relaxation in 84 operations. The operations were of varying type but more than half of them were partial gastric resection, cholecystectomy or exploratory laparotomy. In 29 operations curare was used to facilitate intratracheal intubation. In 9 operations curare was used as an aid to spinal anesthesia and as an aid in 6 bronchoscopies and 2 esophagoscopies. Small doses were also used to relieve hiccoughs during general anesthesia.

In bronchoscopy 40 to 60 units of curare were administered along with thiopental and oxygen. In cases where large initial doses of curare produced bronchial spasm 15 gr. of aminophylline administered intravenously over a period of 5 minutes relieved the spasm. In major surgery in which nitrous oxide and oxygen were used as the major anesthetic agents doses of 100 to 140 units of curare were given during induction and preparation for incision and then doses of 20 to 40 units were given, as necessary, every 30 to 45 minutes

to maintain muscular relaxation. The author pointed out that somewhat smaller doses were used with ether but that nitrous oxide and oxygen was the preferred anesthetic.

Following the operative period if there was evidence of profound curarization as shown by the impairment or absence of costal breathing, 1 or 2 cc. of neostigmine methyl sulfate 1:2,000 was given intravenously.

The author pointed out that patients known to have or suspected of having myasthenia gravis should not be given curare.

The Effect of Dimercaprol in Acute Iron Poisoning. N. D. Edge and G. F. Somers. *Quart. J. Pharm. and Pharmacol. 21*:364 (1948). Recently it was shown that excessive doses of soluble iron salts were toxic to test animals. Since children, particularly, occasionally take large doses of iron salts accidentally the authors studied the value of dimercaprol (BAL) as an antidote for iron poisoning.

The authors used mice as test animals and first established the LD50 for dimercaprol when given orally and intravenously. Then safe doses were determined for use as the antidote dosage. In addition control mice were given the antidote dose of BAL alone during the study. When the BAL was given 15 minutes after large doses of ferrous sulfate and ferric chloride, orally, there was an increase in the toxicity of the iron salts. When BAL was given 15 minutes before the iron salts there was an increase in toxicity with the ferric chloride but a slight lowering of toxicity with ferrous sulfate. The oral dose of BAL in each case was 100 mg. per Kg. of body weight. Intravenously BAL was given in a dose of 50 mg. per Kg. of body weight and there was an increase in the toxicity of both the iron salts.

As a check the protective action of dimercaprol against mercuric chloride was determined in the mice. The toxicity of the mercury salt was decreased several fold both by oral and intravenous administration. This verified previous findings.

Apparently a ferrous-dimercaprol complex accounts for some of the toxicity, at least when given intravenously. When 0.05 M solutions of ferrous sulfate and dimercaprol were mixed in equal por-

tions and then injected there was an increase in toxicity over ferrous sulfate alone.

Thus the authors showed that dimercaprol is not an effective antidote against toxic doses of iron salts.

Experimental and Clinical Observations on Aureomycin. M. Bryer, E. B. Schoenbach, C. A. Chandler, E. A. Bliss, and P. H. Long. *J. A. M. A. 138:*117 (1948). The new antibiotic aureomycin is derived from a strain of *Streptomyces aureofaciens.* The hydrochloride is yellow in color, soluble in distilled water, but less soluble in isotonic sodium chloride solution. The pH of its solution is 4.5. In alkaline solutions the antibiotic activity is reduced rapidly.

Aureomycin has been shown to be antibacterial against numerous gram-positive and gram-negative bacteria such as hemolytic streptococci, *Streptococcus faecalis, Diplococcus pneumoniae,* staphylococci, *Bacillus coli aerogenes, Klebsiella pneumoniae, Hemophilus influenzae,* and *Brucella suis.* Human serum seems to inhibit the effectiveness of the antibiotic. Concentrations of the antibiotic found in the serum ranged from 0.3 to 2.4 micrograms per cc. High concentrations were found in the urine but none in the spinal fluid. In studies on mice the LD_{50} on subcutaneous injection was between 3,000 and 4,000 mg. per Kg. of body weight, while intravenously it was between 50 and 100 mg. per Kg.

Aureomycin produced favorable response in human beings in cases of Rocky Mountain spotted fever, *Escherichia coli* infection of the urinary tract, brucellosis, and typhoid. The antibiotic was given orally in doses of 10 to 60 mg. per Kg. of body weight a day divided into 6 to 12 doses, or intramuscularly in doses of 3 mg. per Kg. divided into 4 doses. There were signs of moderate local irritation following the intramuscular injections.

BOOK REVIEW

Distillation and Rectification. By Emil Kirschbaum. Translated by M. Wulfinghoff. Chemical Publishing Co., Inc., New York, 1948; 426 pp., $10.

This is a book written primarily for the chemist or engineer interested in the design of technical distillation units. It is a translation of a German book copyrighted in 1940.

The first section takes up the study of distillation diagrams for binary and ternary systems, the subject of partial condensation and the effect of pressure on distillation.

Naturally, a great portion of the book is concerned with rectification. Among the subjects studied are: separation of binary and multi-component systems, the use of bubble-cap plates, sieve plates and packed columns. A section is devoted to methods of estimating the number of plates for a given separation as well as the heat requirements. There are also a few pages on Molecular Distillation.

Equilibrium data for 52 binary mixtures, as well as physical properties of some commonly distilled liquids are given in the appendix. In an endeavor to bring the book up to date, the translator has added 16 pages of material abstracted from more recent distillation literature.

It would seem as though the standard American treatises on Chemical Engineering would be more suitable than this book for a beginner starting the study of distillation theory.

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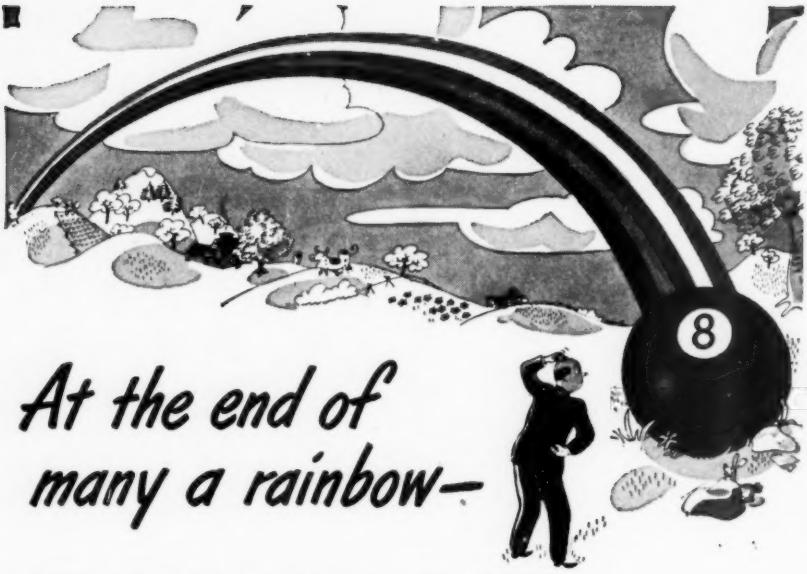

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